Remarks

Claims 1, 4, 16 and 20-34 are pending. Claims 15 and 19 have been cancelled. Claims 1, 16, 20, 21, 22 and 28 have been amended. Claims 31 to 34 are new claims. Support for the amendments and new claims may be found throughout the specification as filed and, for example, for the amendment of Claims 1 and 28 at page 1, lines 5 to 7 and Claim 15 as filed; for new Claims 31 and 32 at page 22, lines 8 to 11; and for new Claims 33 and 34 at page 22, lines 6 to 9. The Applicants respectfully request entry of the amendment and new claims which are believed to place the application in better condition for allowance.

Claims 1, 4, 16 and 20-30 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Claims 1, 4, 16 and 20-30 satisfy the written description requirement. Reasons are set forth below.

The Applicants respectfully submit that the compounds of those rejected claims (antibodies which bind to the beta 1 integrin molecule in a region of amino acid residues 82 to 87 comprising residues TAEKLK and modulate the function of beta 1 integrin) are described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed subject matter. In response to the Examiner's helpful comments that the specification does not describe an actual reduction to practice of a compound that modulates beta 1 integrin through its binding to TAEKLK other than the monoclonal antibody produced by the commercial clone JB1a, the Applicants submit that so far as the Applicants are aware the monoclonal antibody produced by the commercial clone JB1a was at the time of filing, and is currently, the only antibody commercially available which is known to bind beta 1 integrin at the region comprising residues TAEKLK. However, the Applicants respectfully submit that it would be known to those skilled in the art that raising another clone to the same sequences will replicate the observed effects of JB1a binding.

In particular, the JB1a antibody which was used by the Applicants to achieve the observed therapeutic effect recognizes the epitope comprising amino acid residues 82 to 87 which lies in the hybrid domain. This epitope was mapped using the short peptide phage display library approach. This approach initially identified two epitopes, amino acid residues 82-87 and 179-184, the latter falling in the A domain. On verification using short synthetic peptides, binding was only achieved to the peptide of the sequence of 82-87 and no binding was observed to 179-184. It is common

knowledge to those skilled in the art that the phage display library approach is only valid for proximally determining linear epitopes and it does not permit the recognition of combinatorial or non-linear epitopes. To permit the recognition of combinatorial or non-linear epitopes, epitope mapping needs to be performed using a single amino-acid mutation approach. The Applicants therefore respectfully submit that those skilled in the art would be aware that raising another clone to the same sequences will replicate the effect of JB1a binding.

Other clones which are known to bind to the same sequences, as quoted in the review by Al-Jamal and Harrison, are SG/7 and SG/19, which were developed by Miyake et al. and which are combinatorial and bind to the amino acid 82 and the amino acid 87 respectively, and the clones C30B and D11B developed by Ni and Wilkins which bind within the 82-87 amino acid epitope. Unlike the JB1a, none of those clones are commercially available. However, the Applicants respectfully submit that those skilled in the art would be aware that use of these clones will replicate the effect of JB1a binding. This is supported by the fact that the published work of Luo et al. shows that clone SG/19 induces an intermediate conformational state of beta 1 integrin similar to that induced by JB1a, as evidenced by the inventors' FRET data for JB1a submitted in the response to the Official Action dated July 28, 2009. Copies of Miyake et al. and Luo et al. are enclosed.

The Applicants therefore respectfully submit that the specification describes the compounds of the claims (antibodies which bind to the beta 1 integrin molecule in a region of amino acid residues 82 to 87 comprising residues TAEKLK and modulate the function of beta 1 integrin) in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of compounds. The Applicants respectfully request withdrawal of the written description rejection.

Claims 1-4, 16 and 20-30 are rejected under 35 USC §112, first paragraph, as non-enabled. Claims 1-4, 16 and 20-30 are enabled. Reasons are set forth below.

The Applicants note the Examiner's acknowledgement at page 4, second paragraph of the Official Action dated January 28, 2010 that the specification is enabling for antibodies that bind TAEKLK of SEQ ID NO:1.

For the sake of completeness, the Applicants respond to the comments on page 6, first paragraph of the Official Action dated 28 January 2010. The rejection states that Al-Jamal and Harrison teach three antibodies that bind to epitope 82-87 of beta 1 integrin, but only JB1a has the

allosteric modulation properties. Table 1 of Al-Jamal and Harrison lists four antibodies as binding to epitope 82-87 of beta 1 integrin. Of these, only SG/19 is described in Table 1 as stabilizing the low-affinity intermediate confirmation of beta 1 integrin. The Applicants respectfully submit that, although not shown in Table 1, the other three listed antibodies also have allosteric modulation properties. There are a number of existing dual functional anti-beta1 integrin antibodies, but the multiplicity of integrin conformation in conjunction with signaling has only become apparent to those skilled in the art in the past decade.

In response to comments on page 7, second paragraph of the Official Action dated 28 January 2010 that the claimed antibody is recited to result in "an alternation in the metalloproteinase balance" and that this relates to opposing endpoints, the Applicants respectfully submit that an alteration in the metalloproteinase balance refers to an increase in certain metalloproteinases and a decrease in other metalloproteinases, for example, an increase in inactive MMP9 and a decrease in MMP1. The skilled practitioner would have a reasonable expectation that the same compounds would achieve such an alteration.

In response to the comments that the claims are directed to any and every tissue repair and tissue injury, the claims as amended are directed to tissue repair and tissue injury where the extracellular matrix is degraded. Working examples have been provided for emphysema, Parkinson's disease, arthritis and Alzheimer's. The Applicants respectfully submit that the breadth of the provided working examples is more than sufficient to show that the claimed methods can be extrapolated to the claimed types of tissue repair and tissue injury where the extracellular matrix is degraded.

In view of the above, the Applicants respectfully submit that one of ordinary skill in the art can readily make and use the claimed subject matter without undue experimentation. The Applicants respectfully request withdrawal of the enablement rejection.

Claims 1, 4, 16, 20-25 and 28-30 are rejected under 35 USC §103(b) as being unpatentable over US Patent Application Publication No. 2003/0109435 (hereinafter "US '435") in view of the declaration by Al-Jamal and Chemicon International catalog no. MAB1965.

US '435 fails to teach all of the elements of those claims. It does not disclose, teach or suggest the use of the JB1a antibody (or other antibodies which bind the same sequences) for promoting tissue repair or treating tissue injury where the extracellular matrix is degraded.

Furthermore, US '435 does not disclose, teach or suggest that specifically targeting the hybrid domain of beta 1 integrin modulates function of beta 1 integrin, nor that targeting the hybrid domain has agonist/antagonist properties (i.e. functional modulation or conformational modulation). Instead, it teaches that inhibition of beta1 integrin using AIIB2 and JB1a amongst other anti-integrin antibodies inhibited neuronal toxicity by inhibiting the formation of amyloid fibrils.

US '435 enlists that toxicity of preformed amyloid fibrils is only evident when added in conjunction with soluble amyloid. The reason given is that the presence of soluble amyloid enhances the cells' ability to form amyloid fibrils. In the Applicants' working examples, no soluble amyloid was added and, as such, targeting the hybrid domain using JB1a could not have inhibited amyloid fibril formation as those fibrils were preformed separately prior to the study, as normally performed by those skilled in the art. There is no disclosure in US '435 that targeting beta1 integrin's hybrid domain could induce cellular repair. According to US '435, no neurotoxicity was observed when neuronal cultures were treated with amyloid fibrils alone.

The Applicants further respectfully submit that upon examination of the staining pictures of the neurons provided in US '435, the cells appear dedifferentiated and, as such, these cells do not behave like a normal cerebral neuron with neurite extension and a distinct cell body. Dedifferentiation is a common event in primary cells isolated from various tissues. Normally, all studies examining effects on primary neurons entail pretreatment with growth factors and activators (NGF, IBMX, TPA) to revert to the neuronal phenotypic cell morphology. Therefore, the cells shown in the examples are not typical neurons and those skilled in the relevant art would not expect to extrapolate any findings to *in vivo* studies.

The Applicants respectfully request withdrawal of the rejection over US '435.

Claims 1, 4, 16, 20-25 and 28-30 are rejected under 35 USC §103(b) as being unpatentable over US Patent No. 6,123,941 (hereinafter "US '941").

US '941 fails to teach all of the elements of the claims. It does not disclose, teach or suggest the use of the JB1a antibody (or other antibodies which bind the same sequences) for promoting tissue repair or treating tissue injury wherein the extracellular matrix is degraded. In US '941, tumor cells were able to synthesize extracellular matrix, albeit disorganized. US '941 claims that targeting the beta1 integrin using AIIB2 enhances normal organization of the matrix leading to an alteration in cell behavior wherein cells revert from a malignant phenotype to a normal phenotype. The

Applicants' claimed compounds are used to promote tissue repair or treat tissue injury where the extracellular matrix is degraded. The Applicants respectfully submit that degradation is higher than synthesis and that use to enhance matrix organization differs from use to promote tissue repair or treat tissue injury where the extracellular matrix is degraded.

The Applicants further respectfully submit that the work of Bissell et al. mainly details the effect of functional inhibition of beta1 integrin in mammary tumor cells *in vitro* using the clone AIIB2, which binds the beta A domain within amino acids 207-218. This was not clearly discerned in the patent but is in the research publications of the data detailed in the patent. US '941 states at column 5, line 64 with respect to the use of AIIB2 that: "Note that T4 cells revert to normal phenotype when beta1 integrin function-blocking antibody (Ab) is applied but that normal cells die as a result of application of the beta1 integrin function-blocking antibody". US '941 therefore teaches that using AIIB2 on non-transformed or non-cancerous cells would in fact increase cell death. The pro-apoptotic effect of AIIB2 on normal human cells would cause serious adverse side-effects. This effect could not have been seen in the *in vivo* experiments in mice as AIIB2 was not shown to cross react with mouse beta1 integrin. The cells to be treated by the Applicants are non-tumor cells which are dying as a result of injury. Furthermore, in the Applicants' emphysema model, there was no histological evidence of proliferation associated with injury or its reversal on the basis of the morphology in the H&E sections used in the patent (Ki67 staining was done on lung sections). Targeting the hybrid domain of beta1 integrin using JB1a, unlike the AIIB2 listed in US'941, prevented apoptosis and has not demonstrated any detectable side effects of such severity in both *in vitro* and *in vivo* studies.

The Applicants respectfully request withdrawal of the rejection.

Claims 1 and 20 stand rejected under 35 USC §103(a) as being obvious over US '941 in view of Owens et al. The deficiencies of US '941 are discussed above. Owens et al. does not remedy these deficiencies. The Applicants therefore respectfully request withdrawal of the rejection.

Claims 1, 4, 16 and 20-30 stand provisionally rejected on the ground of nonstatutory double patenting over Claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of copending Application No. 12/528,749. The Applicants respectfully submit that because the rejection is provisional, they will address it when the rejection becomes non-provisional.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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